CALCIFIC UREMIC ARTERIOLOPATHY (CALCIPHYLAXIS)

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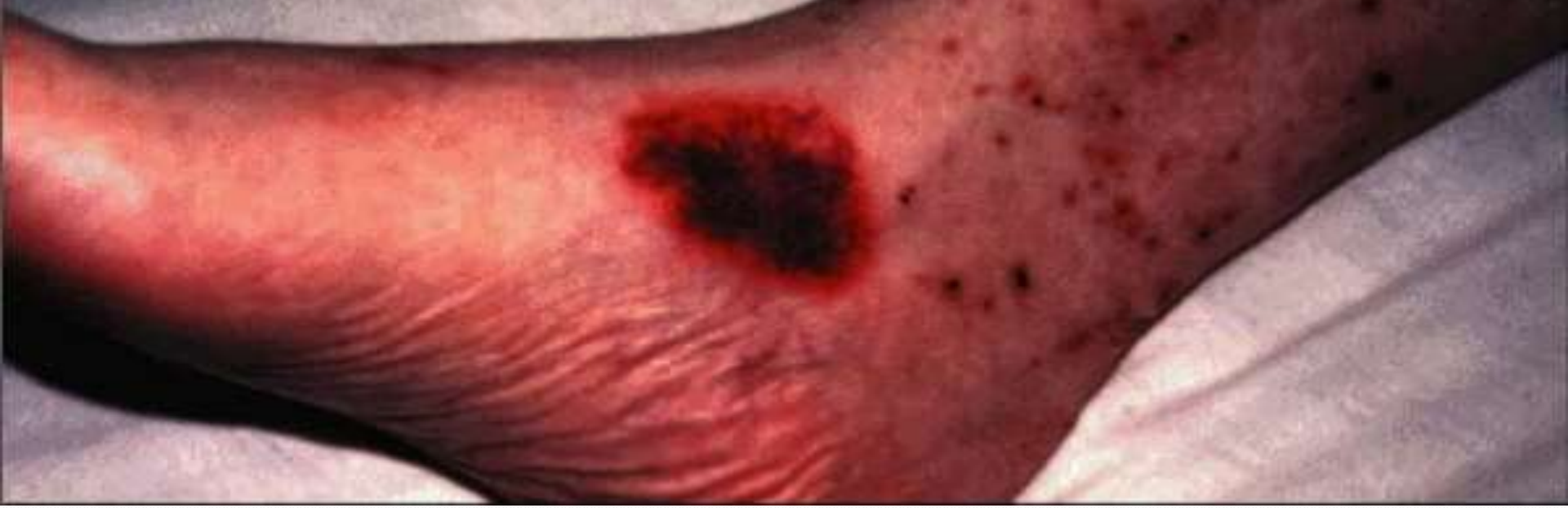
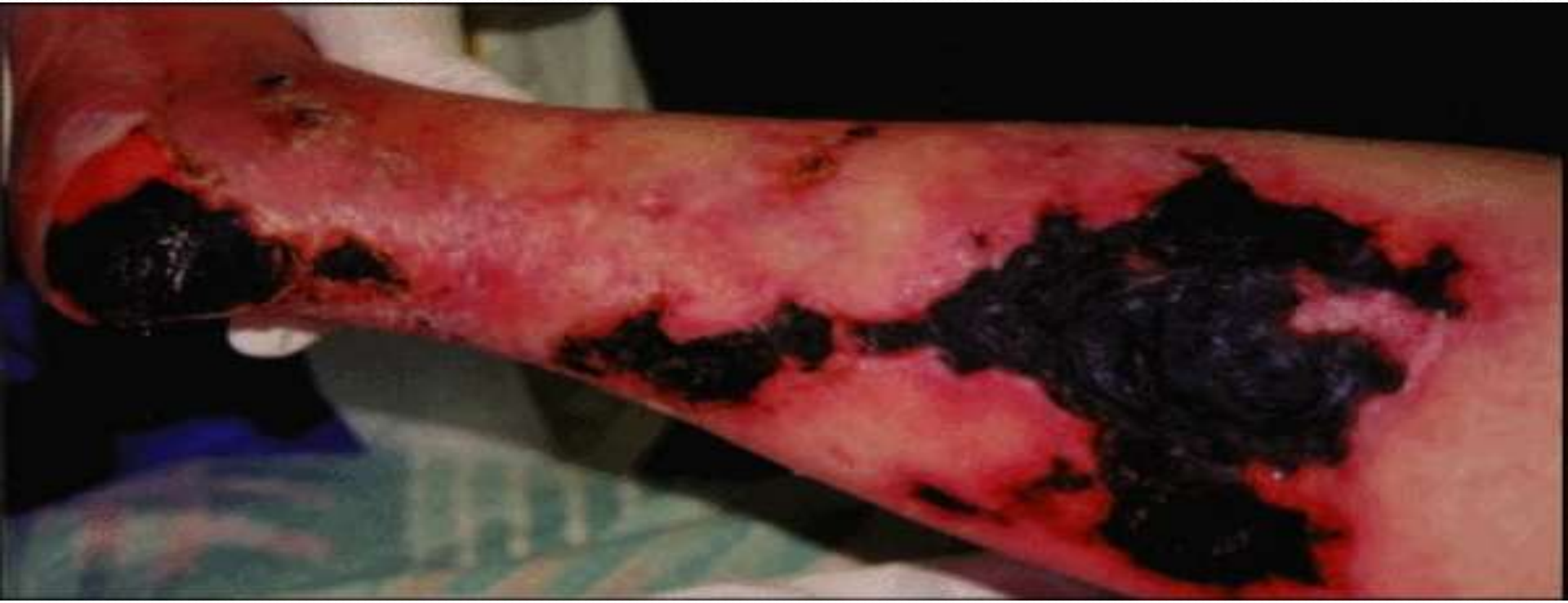




- Calciphylaxis is a poorly understood and highly morbid syndrome of vascular calcification and skin necrosis. Bryant and White first reported it in association with uremia in 1898.

- In 1962, Selye constructed an experimental model and was able to precipitate systemic calcification, somewhat analogous to this syndrome, in nephrectomized rats. He was the first to coin the term calciphylaxis to characterize this enigma.

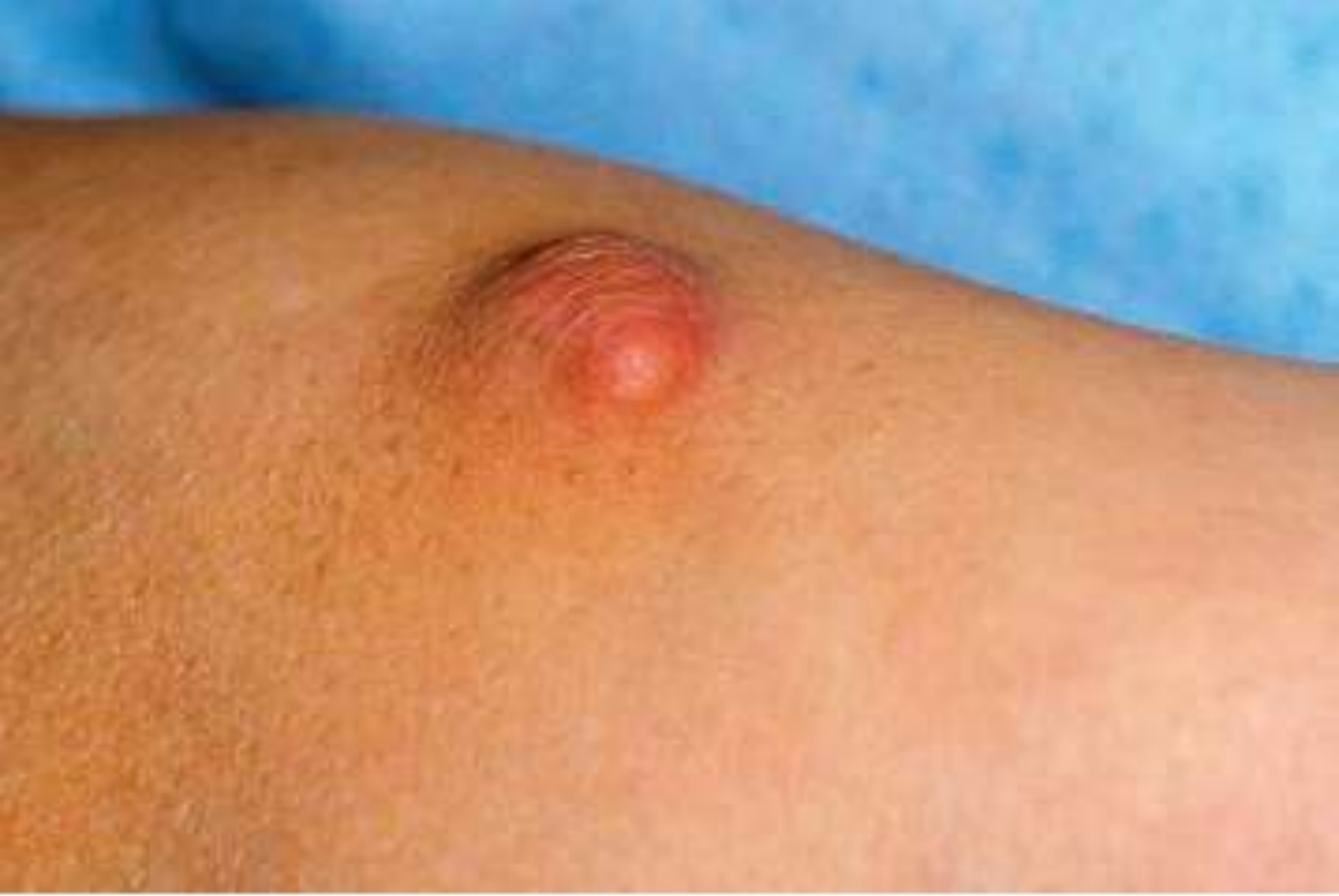
Definition

- Calcific uremic arteriolopathy (CUA), or calciphylaxis, is a devastating and life-threatening ischemic vasculopathy confined primarily to patients with CKD.

- The ischemia may be so severe that frank infarction of downstream tissue develops.

- The most common and most noticeable damage is in the skin and subcutaneous tissues.

- CUA should be distinguished from benign nodular calcification (calcinosis cutis) which can develop in patients with very high serum calcium-phosphate product.



Benign nodular calcification (calcinosis cutis). Firm subcutaneous nodule adjacent to the elbow.

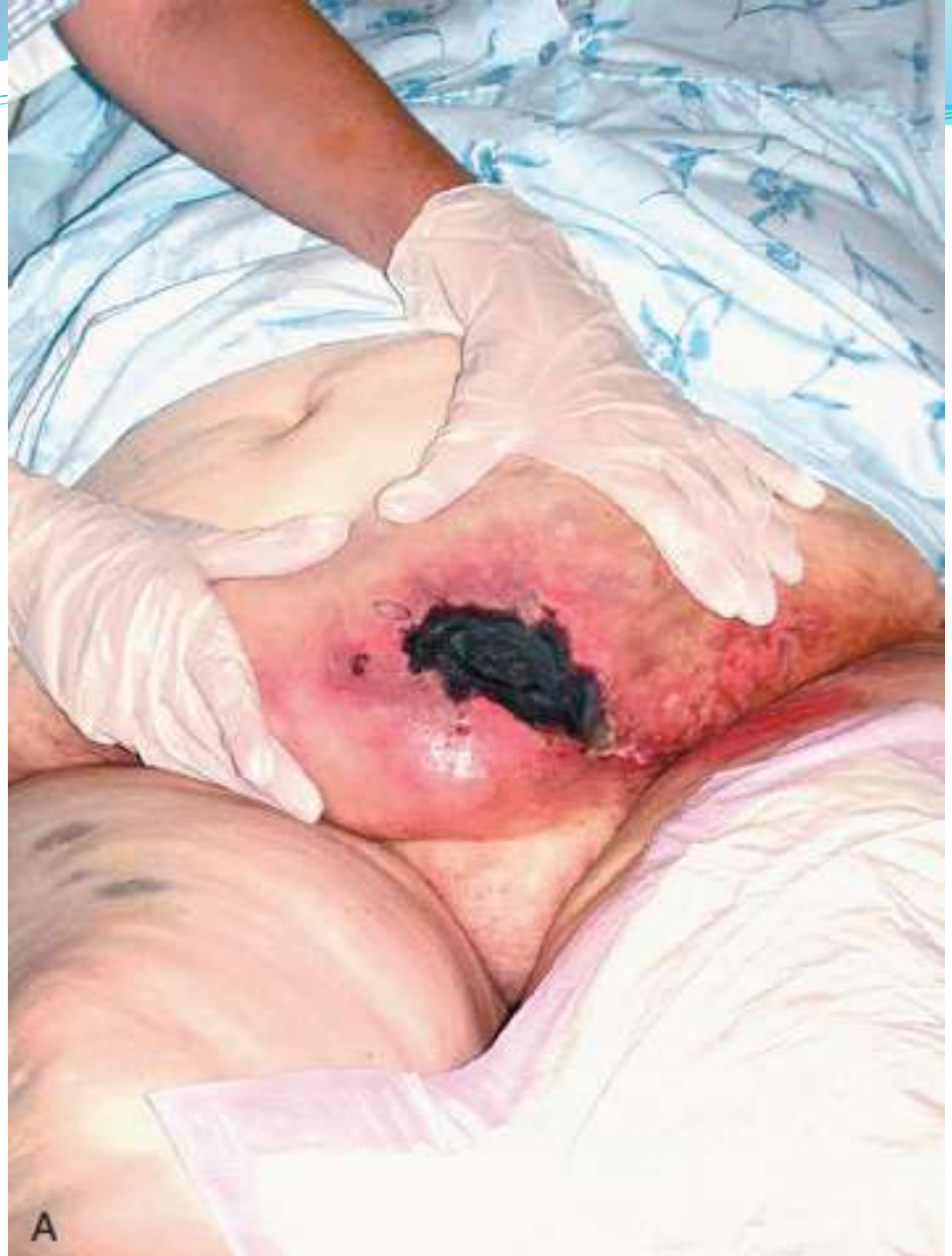
Epidemiology and Risk Factors

- The incidence of CUA may be increasing.
- The estimated incidence ranges between 1 and 4 per 100 patient-years.
- This might be due in part to increased physician awareness and possibly the practice of treating severe hyperparathyroidism with calcium-based phosphate binders plus vitamin D analogues.

- Long-term obesity
- Recent and sudden weight loss
- Malnutrition
- Infusion of medications such as iron dextran
- Remote and/or recent use of immunosuppressive agents, especially corticosteroids
- Liver disease
- Diabetes mellitus and insulin injections
- Use of vitamin D and calcium-based phosphate binders
- Elevated aluminum levels
- Concomitant vascular disease
- Concurrent use of warfarin anticoagulation: Current data suggest that warfarin therapy may lower protein C concentrations, leading to a procoagulant condition in the calcified vessel. Warfarin may also inhibit carboxylation of matrix Gla protein, an important inhibitor of calcification, thus promoting calcification

Clinical Manifestations

- CUA is frequently precipitated by a specific event, such as local skin trauma or a hypotensive episode.
- CUA is typically characterized by areas of ischemic necrosis of the dermis, subcutaneous fat, and, less often, muscle.
- These ischemic changes lead to livedo reticularis or violaceous, painful, plaque-like subcutaneous nodules on the trunk, buttocks, or proximal extremity, that is, in areas of greatest adiposity (proximal CUA).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- Most patients with calciphylaxis have a long-standing history of chronic renal failure and renal replacement therapy. On rare occasions, calciphylaxis may occur in a patient with chronic renal failure prior to the initiation of replacement therapy. Very rarely, it may occur in an individual without a history of chronic renal failure.

- Frequently, patients have been noncompliant with dietary, medical, and/or dialysis prescriptions prior to the onset of calciphylaxis.

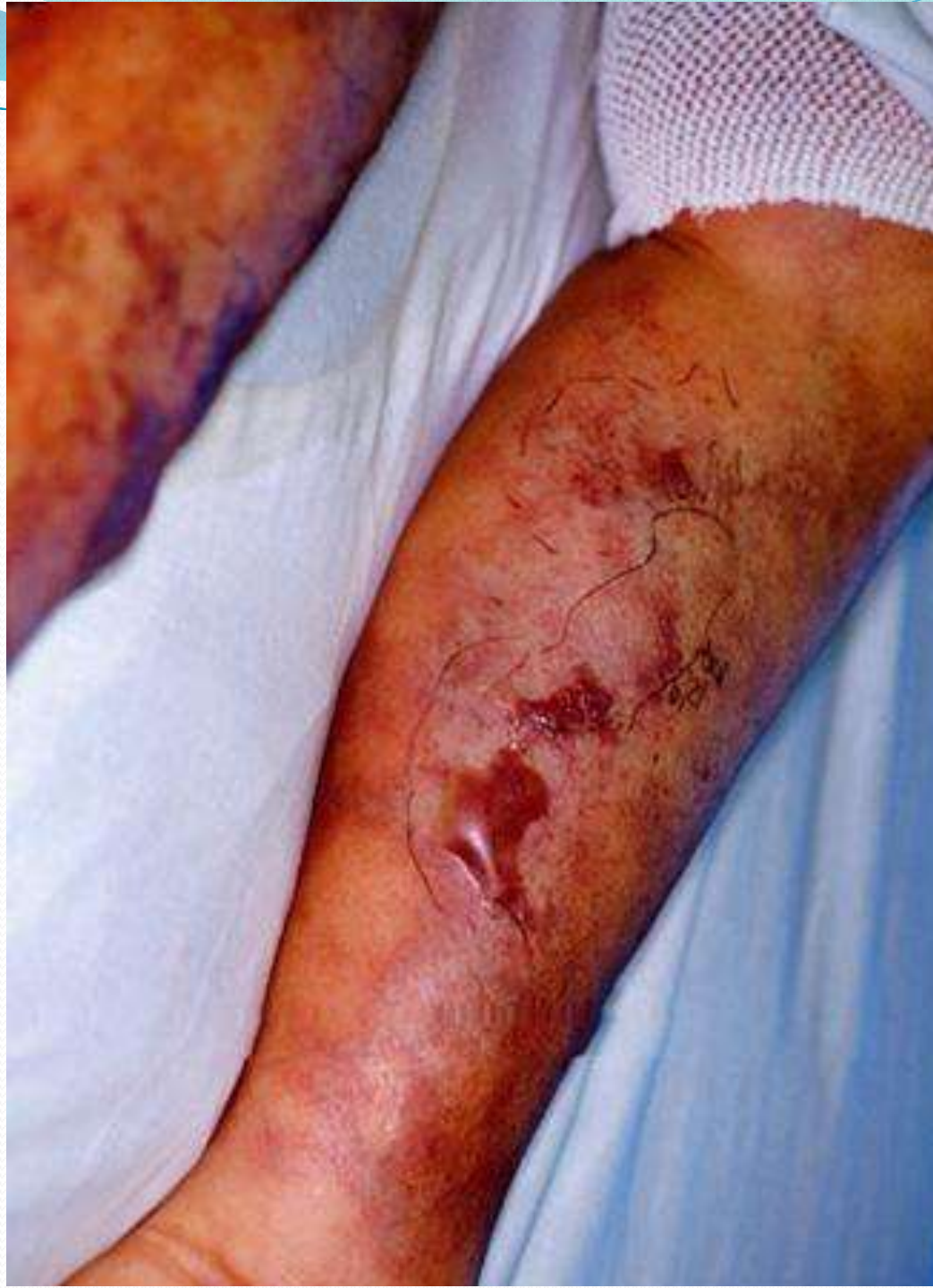
- Many persons who develop calciphylaxis have undergone renal allograft transplantation. The allograft may still be functional when calciphylaxis develops.

- Patients with nonuremic calciphylaxis frequently have a history of primary hyperparathyroidism, malignancy, alcoholic liver disease, or underlying connective-tissue disease or pro-inflammatory condition.

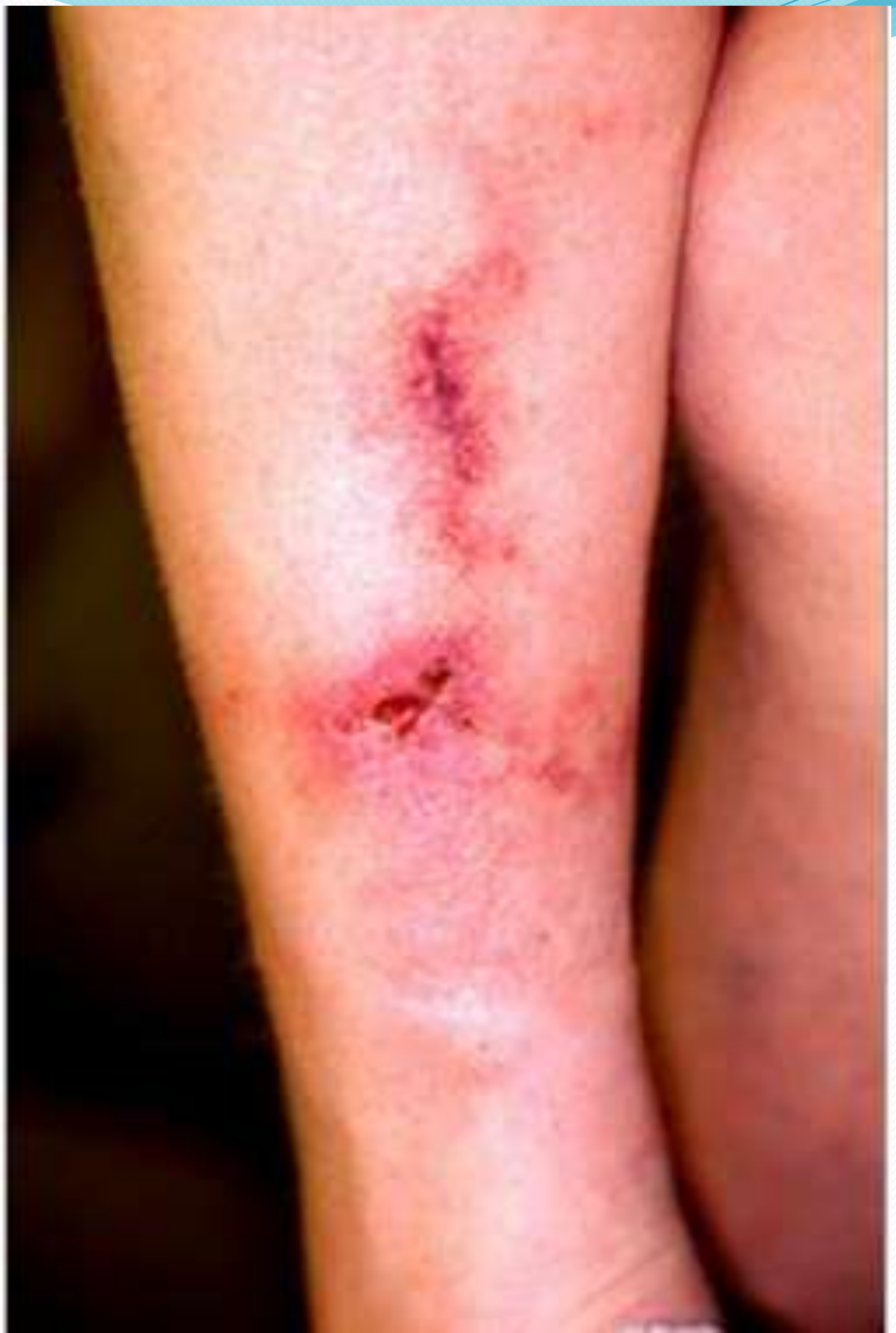
- CUA can also affect the hands, fingers, and lower extremities, thereby mimicking atherosclerotic peripheral vascular disease (distal CUA).

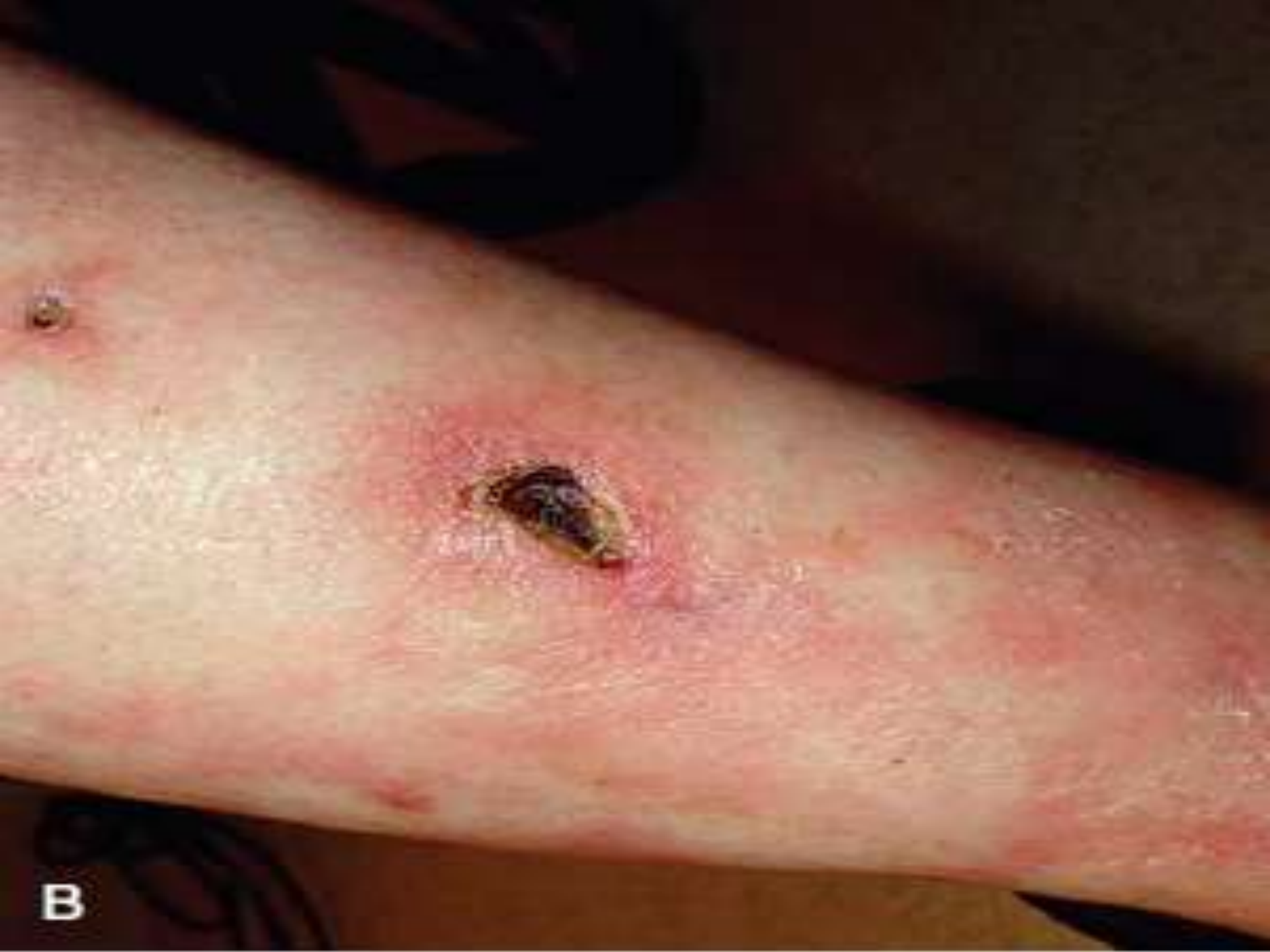
- Lesions of calciphylaxis typically develop suddenly and progress rapidly. Lesions may be singular or numerous, and they generally occur on the lower extremities; however, lesions also may develop on the hands . Intense pain is a constant finding.

Calciphylaxis may manifest as rapidly progressive, diffuse and extensive, cutaneous necrosis, as is seen in this patient with chronic renal failure. Bullae may also be seen as a rare manifestation of calciphylaxis.



Several lesions of calciphylaxis that occurred on the lower extremity of a patient undergoing dialysis. These lesions developed in areas of livedo reticularis and followed the path of the vasculature.

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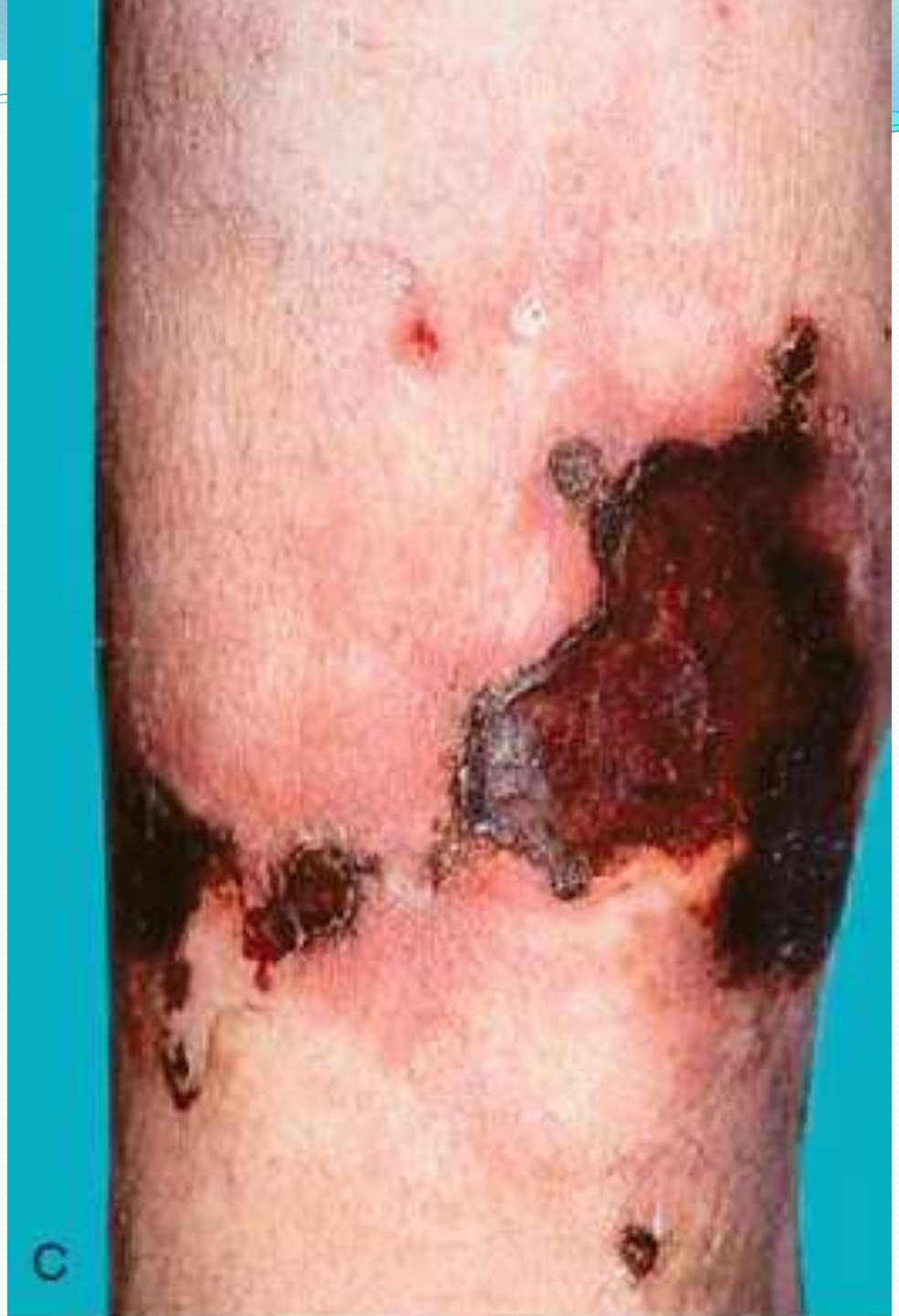
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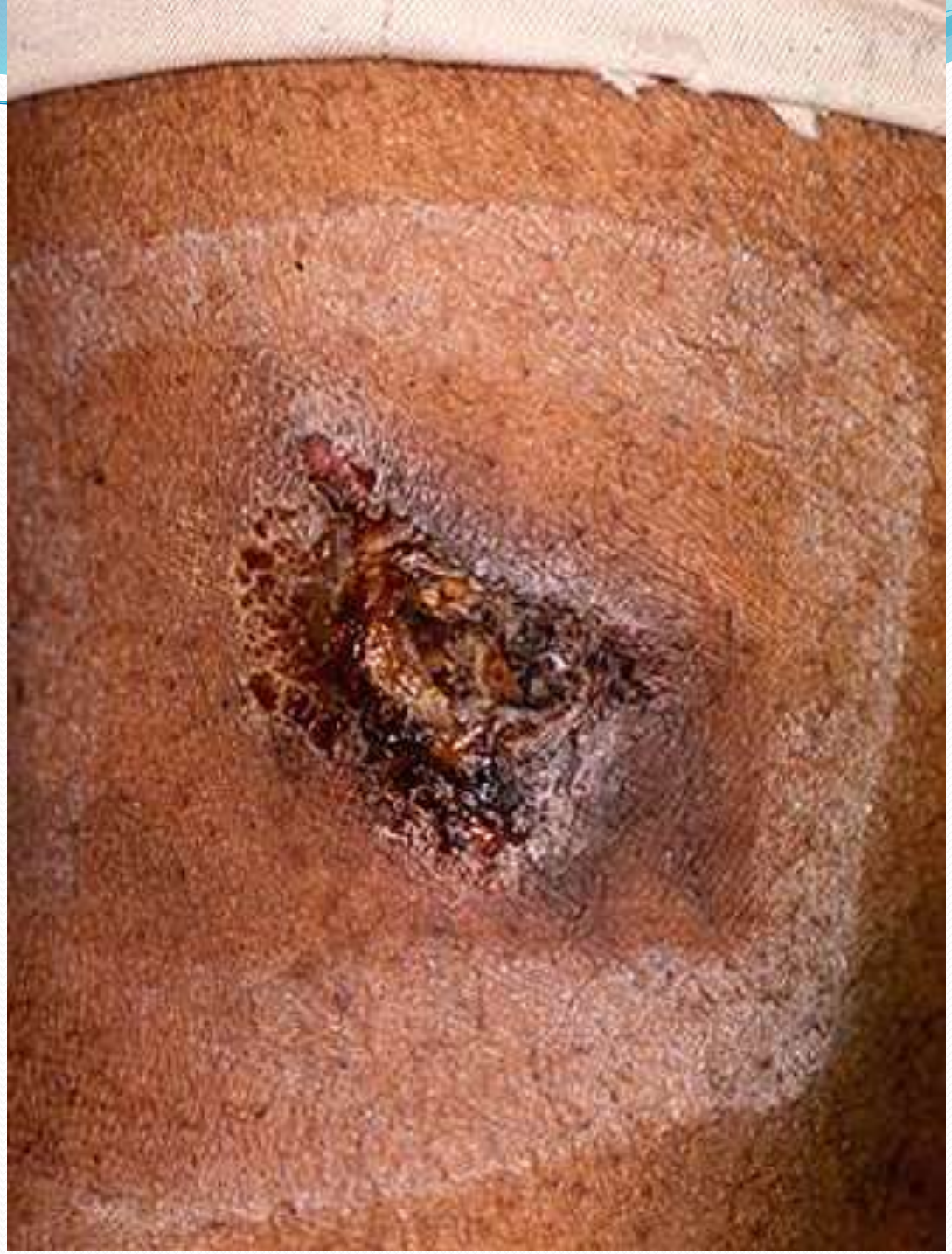
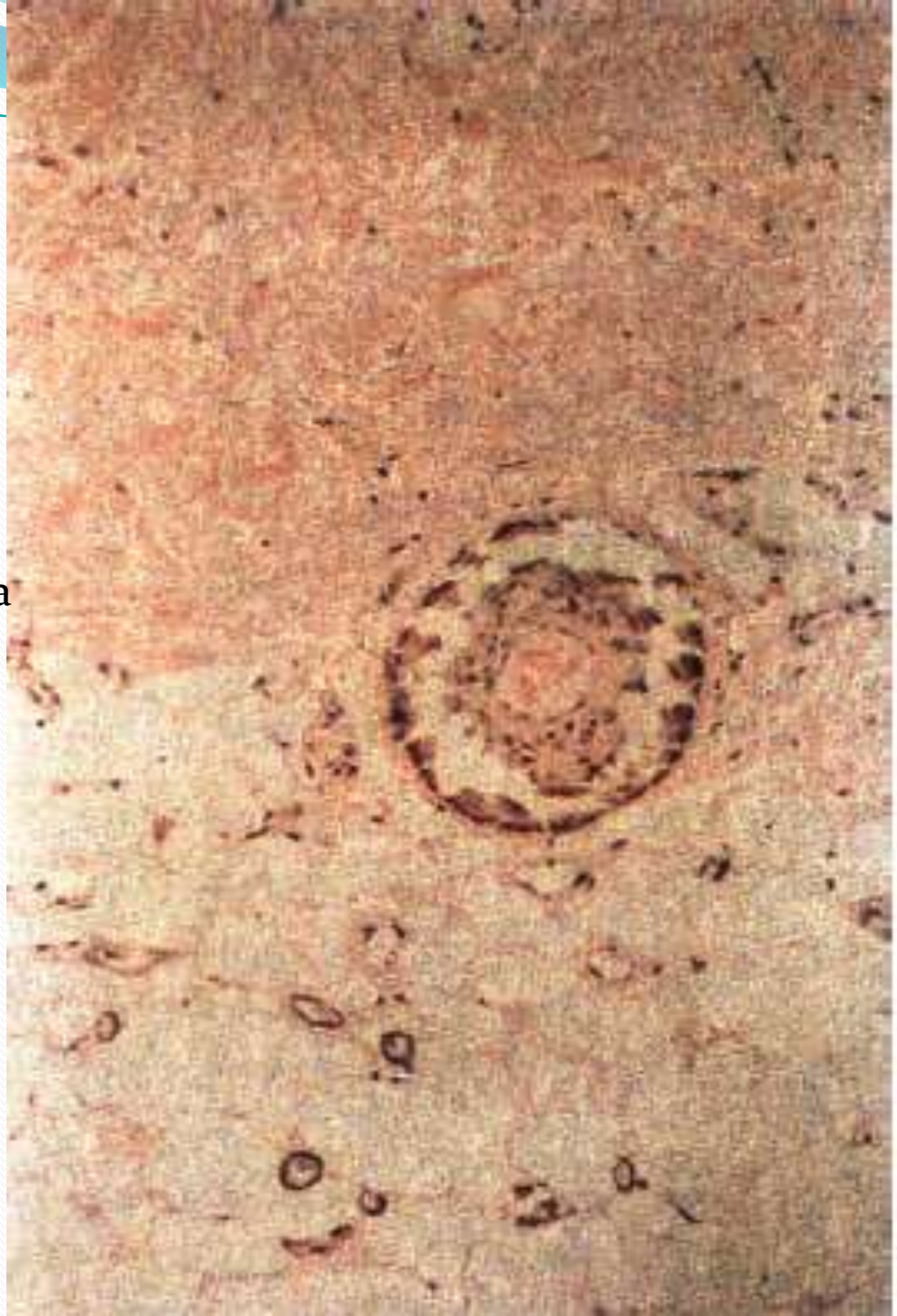
An isolated lesion of calciphylaxis manifesting as an enlarging necrotic plaque on the lower extremity of a patient undergoing dialysis. The stellate purpuric morphology can be appreciated surrounding the area of necrosis.

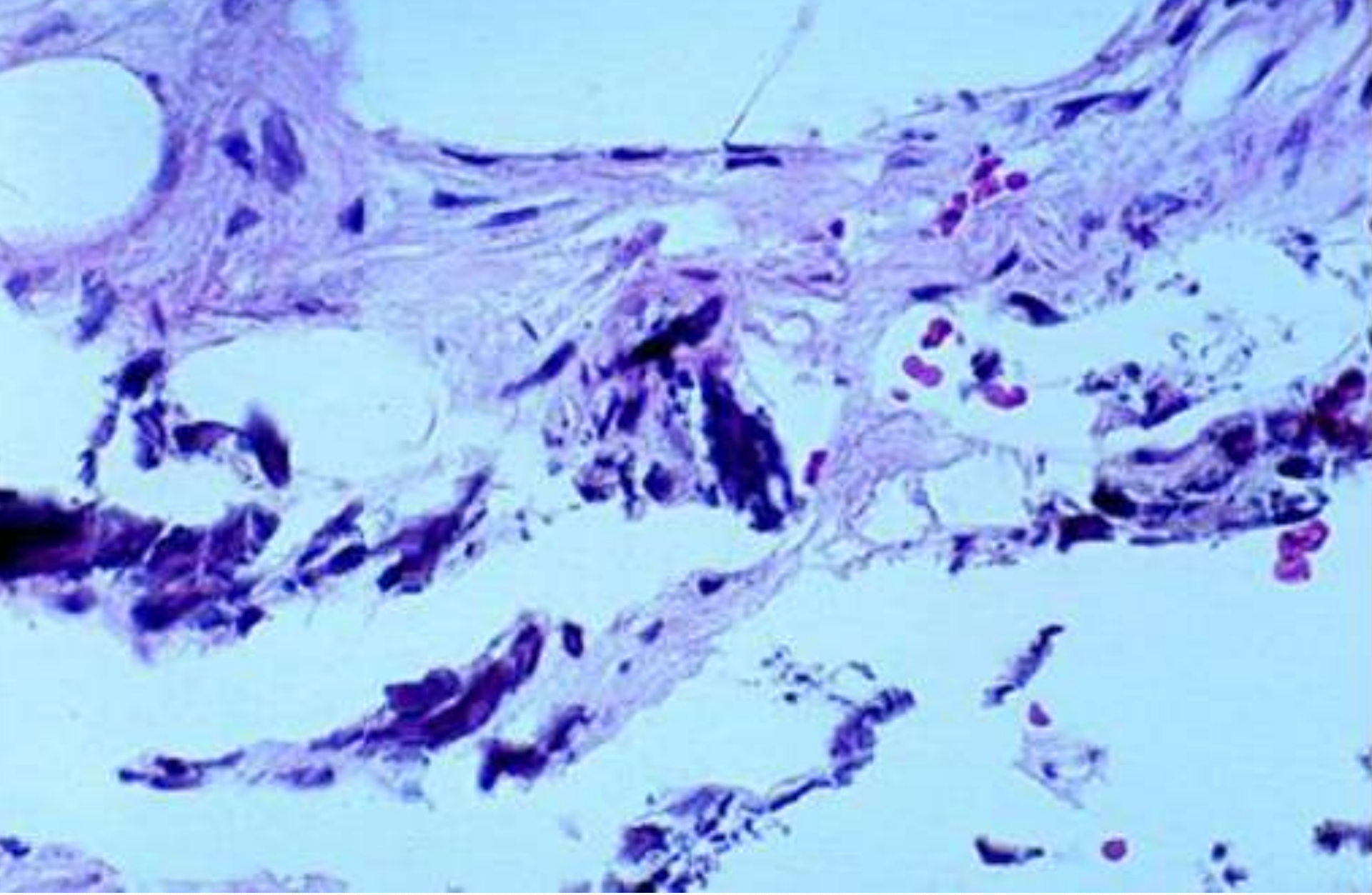


Pathology

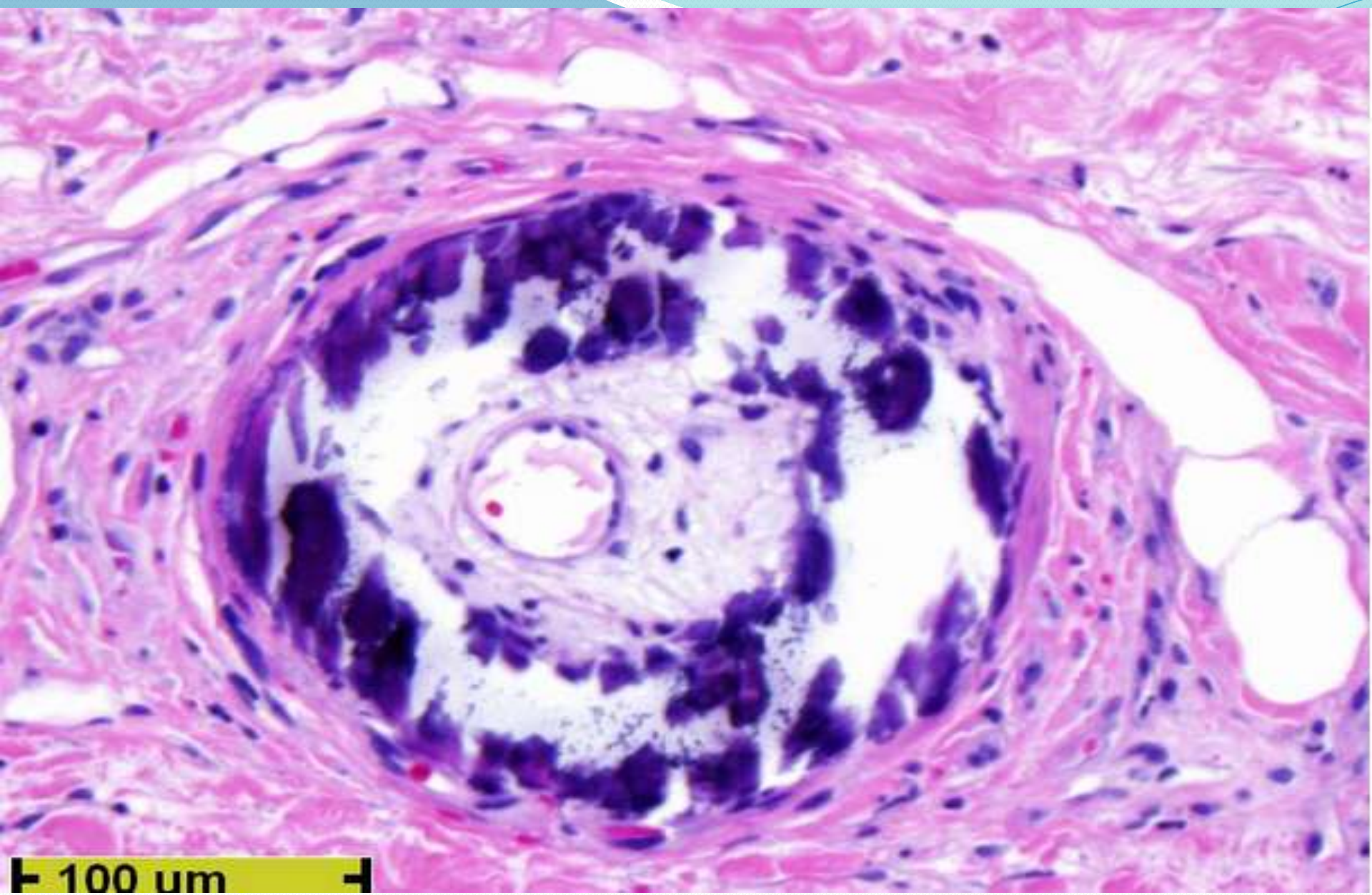
- The histologic features of CUA are suggestive but not pathognomonic.
- Specimens from incisional biopsies of early lesions show subtle histologic changes.
- Late lesions characteristically show epidermal ulceration, dermal necrosis, and mural calcification with intimal hyperplasia of small and medium-sized blood vessels in the dermis and subcutaneous tissue.

Histopathologic features of calcific uremic arteriolopathy.
Medial calcification and intimal hyperplasia of an arteriole at the dermal-subcutaneous junction. Note calcification of interlobular capillaries in the subcutaneous tissue *(arrows)*. Van Kossa staining.

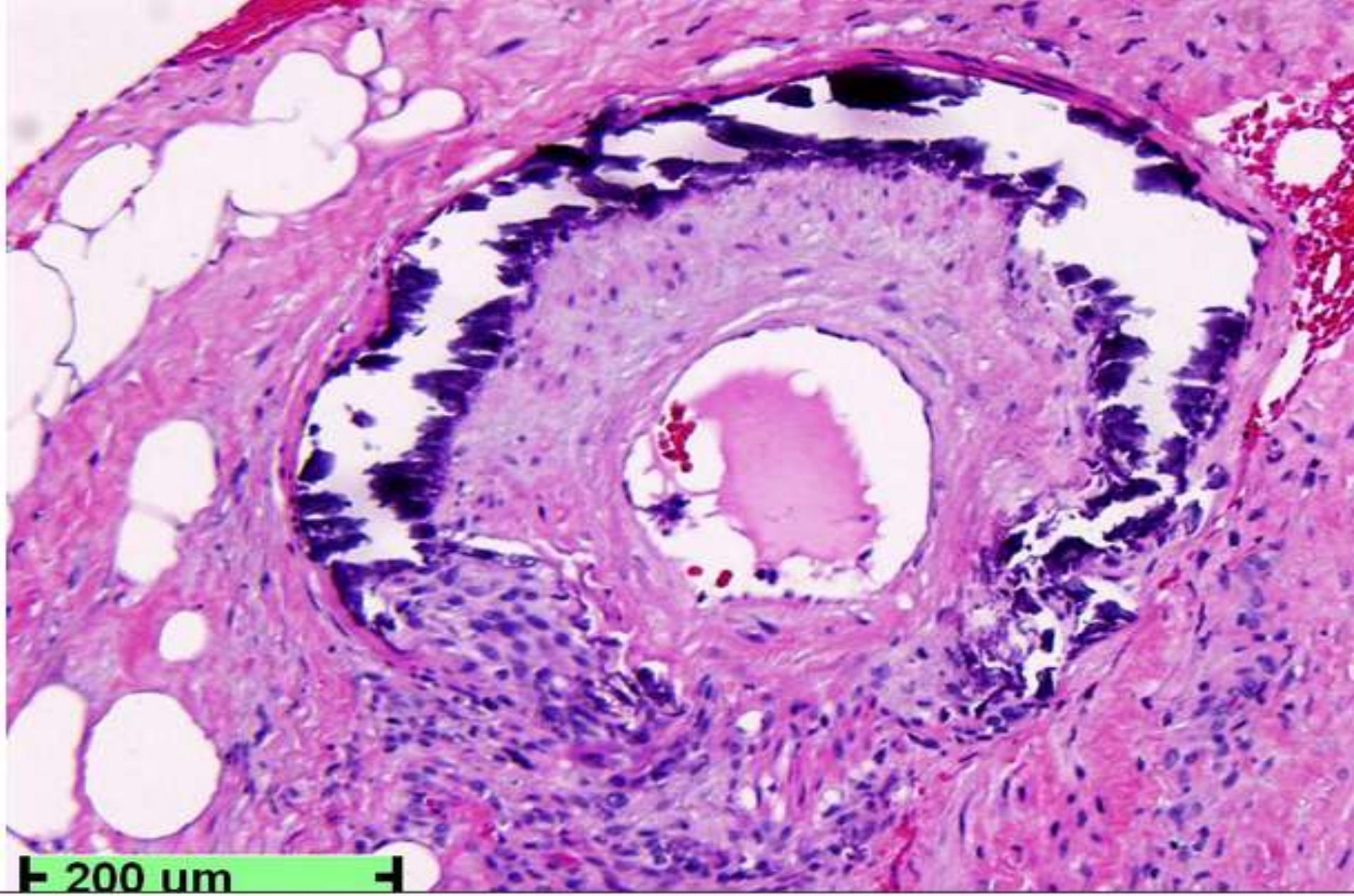




Histologically, calcification of the blood vessels, as well as the subcutis, can be seen in calciphylaxis.



Demonstrated here is the characteristic circumferential medial calcific deposit in an arteriole with subintimal edema. Histologic images courtesy of Steve A. McClain, MD, Department of Dermatology SUNY-Stony Brook.



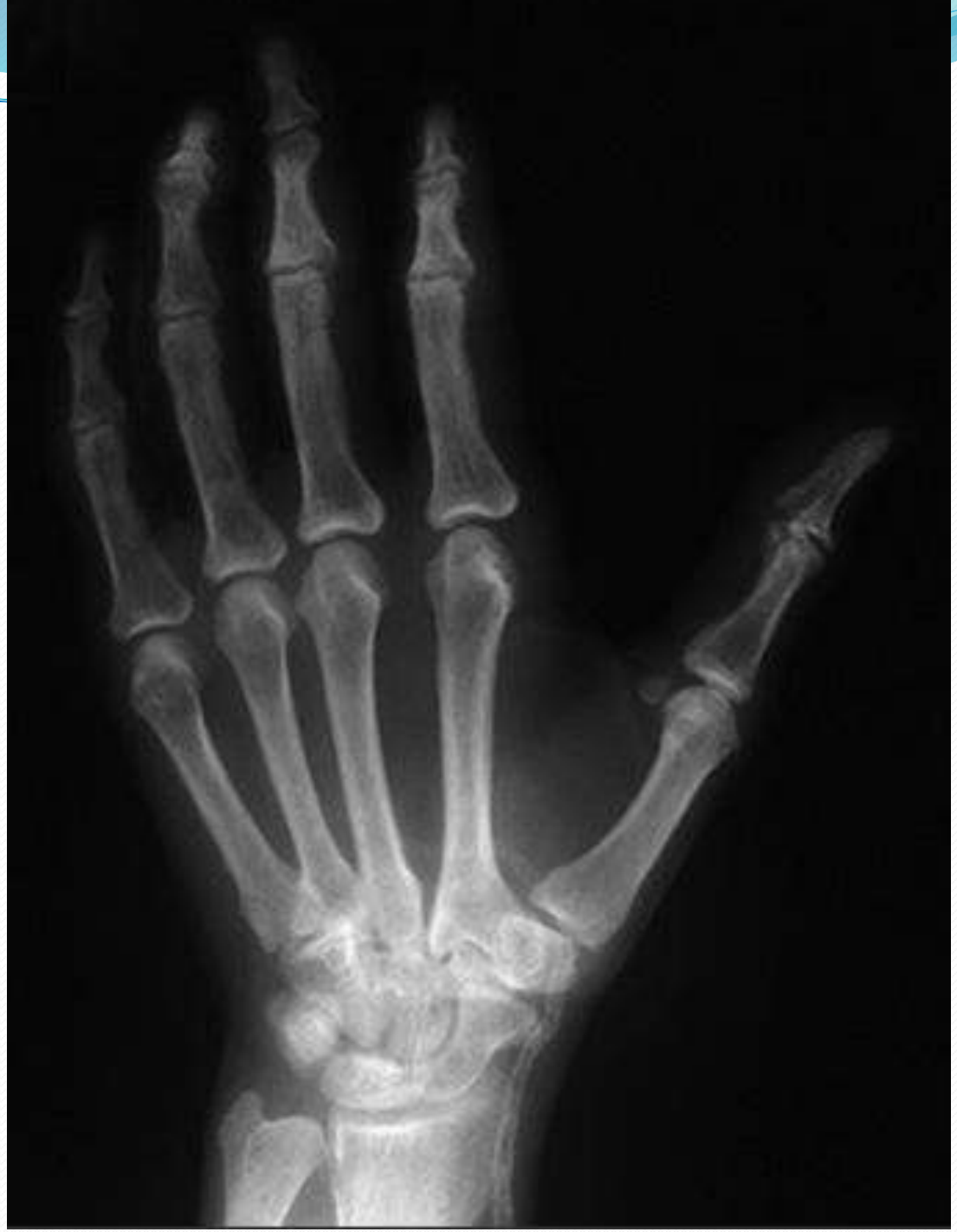
This image shows circumferential medial calcific deposits obliterating the external elastica of an arteriole. Histologic images courtesy of Steve A. McClain, MD, Department of Dermatology SUNY-Stony Brook.

Diagnosis

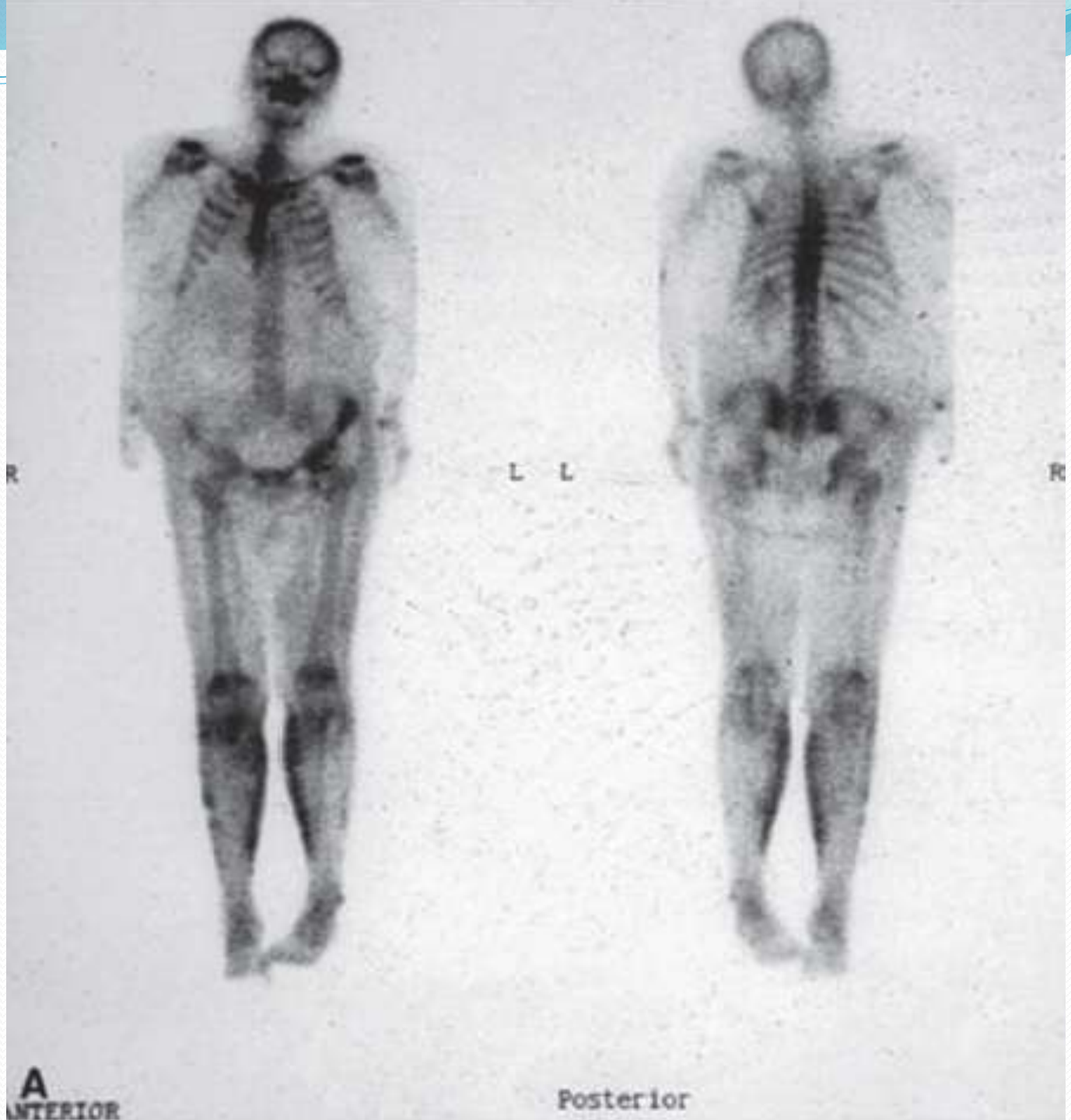
- Although ulceration is an obvious presentation of CUA, increasing awareness of the condition should allow diagnosis at an earlier, nonulcerative stage.
- Biopsies are discouraged because of potential ulceration in the region of the incision and the risk of sample error.
- Many clinicians base the diagnosis of CUA on physical examination findings only.
- Other potentially useful diagnostic procedures include measurements of transcutaneous oxygen saturation, bone scintigraphy , and xeroradiography.

- Plain radiography uniformly demonstrates an arborization of vascular calcification within the dermis and the subcutaneous tissue. Although calcification is common in persons with end-stage renal disease, and not specific for calciphylaxis, a recent study showed patients with calciphylaxis had more vascular calcifications, more small vessel calcifications, and a netlike pattern of calcifications. This netlike pattern, when present, was strongly associated with the presence of calciphylaxis

Radiologic findings of a hand in a patient with calciphylaxis. Extensive calcification of the radial and ulnar arteries is readily visible.



Bone scintigraphic abnormalities in calcific uremic arteriolopathy.
Calf calcification in a patient with gross ulcerations in both legs from the popliteal fossae to the ankles



Differential Diagnosis

- The following conditions should be considered in the differential diagnosis:

- systemic vasculitis, peripheral vascular disease, pyoderma gangrenosum, atheroemboli, cryoglobulinemia, warfarin-induced skin necrosis, and systemic oxalosis.

Natural History

- Despite intensive combined treatments, the prognosis of CUA remains poor; the overall 1-year survival is 45% and the 5-year survival is 35%, with a relative risk of death of 8.5 compared with other dialysis patients.
- Patients with ulcerative or proximal CUA have the worst prognosis. Infection accounts for up to 60% of the mortality.

Prevention and Treatment

- Preventive approaches include attention to calcium, phosphorus, PTH homeostasis, and nutritional state.
- Aggressive program of wound care and prevention of superinfection, adequate pain control, and correction of underlying abnormalities in serum calcium and phosphorus concentrations.
- This includes cessation of vitamin D supplementation, intensification of the dialysis regimen, and use of a low-calcium dialysate and non–calcium-containing phosphate binders (e.g., sevelamer, lanthanum carbonate).
- Furthermore, local tissue trauma, including subcutaneous injections, should be avoided.

- Vitamin K supplementation is advised in patients with warfarin- or coumarin associated CUA.
- Novel and promising therapies include sodium thiosulfate and bisphosphonates.
- Sodium thiosulfate has recently been licensed as drug for CUA by the European Medicines Agency. It enhances the solubility of calcium deposits because exchange of calcium for sodium results in extremely soluble calcium thiosulfate. Besides being a chelator of calcium, sodium thiosulfate is also a potent antioxidant. Sodium thiosulfate is given intravenously at the end of every HD session (12.5 to 25 g during 30 to 60 minutes).

- Apart from nausea and vomiting, the therapy is well tolerated. The major side effect of sodium thiosulfate infusion is the development of metabolic acidosis. The optimal duration of treatment and potential effects of long-term treatment on bone are unknown.


Thank You!